Hybrid Latent Class Measurement of Health States Lacking a Gold Standard

Karen Bandeen-Roche\textsuperscript{1} 
Jeannie-Marie Sheppard\textsuperscript{2} 
Jing Ning\textsuperscript{1} 
Departments of Biostatistics\textsuperscript{1} and Mental Health\textsuperscript{2} 
Johns Hopkins Bloomberg School of Public Health

ENAR Spring Meeting 
Atlanta, Georgia 
March 13, 2007
Measurement problem

- A health state
  - recognizable
  - conceptually well defined
  - has known consequences

- No gold standard
  - more than diagnostic error
  - no single consensus measurement
  - multifaceted consequences
Measurement Problem
Geriatric Frailty

Fried et al., J Gerontol 2001; Bandeen-Roche et al., J Gerontol, 2006
Measurement Problem
Aging

- Recognition
  - Chronic disease, disability, events
  - Variability among individuals
- Theory: a biological process
  - More than consequence accumulation
  - Multisystem dysregulation
- No gold standard
  - Even to the point of "surrogates"
Successful measures
Classical Approach: Validity

- **Face**: recognition
- **Content**: facets covered
- **Criterion**: utility
- **Construct**: theory
  - internal; external

*DeVellis, 1991; Bartholomew, 1996*
Points of the Introduction

• A well defined target; a less-well-defined operationalization

• Will retain validation for measure definition; performance evaluation

• Objective: Method to unify multiple validation aspects in 1 analysis
Outline

• Latent variable paradigm for measurement

• A new idea
  – Aims to balancing potentially conflicting validation premises
  – Application

• Discussion
Measurement
Latent Variable Paradigm

\[ \text{Determinants} \]

\[ \text{Pro-inflammation} \]

\[ \text{Adverse outcomes} \]

\[ e_1 \]

\[ Y_1 \]

\[ \ldots \]

\[ e_p \]

\[ Y_p \]
Model

Generic

Specific (Latent Class Reg.; Categorical U=j, \{1,\ldots,J\})

Measurement assumptions: \[ Y_i | U_i, x_i \]

- conditional independence, nondifferential measurement

> heterogeneity in criterion presentation unrelated to measured or unmeasured characteristics

> fundamentally identifying
Latent Class Measurement

How to obtain “indices”?

• Via posterior probabilities of class membership =

\[ \hat{F}_{U|Y,x}(u \mid y, x) \]

• Then: exactly how?
  – “Modal”: by highest probability
  – “Pseudo-classes”: Randomize (Bandeen-Roche et al., 1997; Wang et al., 2005)
In what sense is LCA a “measurement” model?

• Does it “discover” structure?

• It operationalizes theory
  – Science: Test if predictions borne out
  – Most frequent theory: Homogeneity
Latent Class Measurement Syndrome Validation Application

• Criteria *manifestation is syndromic*

  “a group of signs and symptoms that occur together and characterize a particular abnormality” (Webster Medical Dictionary 2003)

• If criteria characterize syndrome:
  - At least two clinically homogeneous groups (if <2, no co-occurrence)
  - No subgrouping of symptoms (otherwise, more than one abnormality characterized)

  Bandeen-Roche et al., J. Gerontol Med Sci, 2006
Measurement Application: Pro-Inflammation

- Central role: cellular repair

- A hypothesis: dysregulation key in adverse aging
  - Muscle wasting (Ferrucci et al., JAGS 50:1947-54; Cappola et al, J Clin Endocrinol Metab 88:2019-25)
  - Receptor inhibition: erythropoietin production / anemia (Ershler, JAGS 51:S18-21)

Stimulus (e.g., muscle damage) → IL-1# → TNF → IL-6 → CRP

# Difficult to measure. IL-1RA = proxy
Rationale of the New Work

• Which deserves pre-eminence?
  – Internally validating assumptions?
  – Externally validating assumptions?
    • Frailty: close tie to systemic dysregulation
    • Depression: genetic “subtypes”
    • Aging: tie to chronological age
  – Some compromise?
Rationale of the New Work

• Which deserves pre-eminence?
  – Internally validating assumptions
  – Externally validating assumptions?
  – Some compromise?

• A model (LCR) including externally validating variables and fitting by ML already “is” a compromise
A representation theorem

- Consider “mixing” & “kernel” distributions:
A representation theorem

- $Y_i$ is equivalent in distribution to $Y^*$ constructed as

  1) Generate $V_i^*$ from $F^*_{V|x}(v|x_i)$

  2) Given $V_i^*$, generate $Y^*$ from $F^*_{Y|V,x}(y|V_i^*,x_i)$

- **Relevance:**
  - True for $\theta^* = \text{Huber (1967) limit of MLE (e.g.)}$
True vs. realized mixing models
Rationale of the New Work

• Which deserves pre-eminence?
  – Internally validating assumptions
  – Externally validating assumptions?
  – Some compromise?

• Proposal: Allow stronger (or weaker) compromise than ML via “penalized” fitting
Implementing penalization

- **On LCR kernel**: Houseman, Coull & Betensky, *BMCS* online early

- **On LCR mixing distribution**: Sheppard Ph.D. thesis

- **Key questions**
  - Form of the penalty
  - Different purpose than usual?
  - What is the objective function?
Penalization

Very brief background

• Fitting: minimize

\[-2 \ln L(\theta; Y, x) + \lambda g(\theta)\]

• Examples
  – “Ridge”: \( g(\theta) = \sum_j \theta_j^2 \)
  – “Lasso”: \( g(\theta) = \sum_j |\theta_j| \)

*Green, Int Stat Rev, 1987; Tibshirani, JRSS-B, 1996*
Penalization
Very brief background

- A useful equivalence: penalized fit obtains via formulating parameters as crossed random effects
  - “Ridge”: $\theta_j \sim N(0,\sigma^2\lambda^2)$
  - “Lasso”: $\theta_j \sim \text{double exp}(0,h\lambda)$

Form of the penalty
Current case

• Usual purpose: regularization

• Here: secondary validation

• Discriminant hypothesis: Genotypes predispose individuals to only one “subtype” of depression
Form of the penalty
Genetic subtypes example

• Say, LCR with one normal class (1) and two disordered classes (2, 3):

• Hypothesis: $\beta_{1j}$ negligible, and $\beta_{1j'}$ appreciable, in

$$\log \left( \frac{p_k}{p_1} \right) = \beta_{0k} + \beta_{1k} x$$

with $p_k = \text{pr(class k)}$; $x =$ genotype indicator; $k = 2, 3$; $j, j' \in \{2, 3\}; j \neq j'$
Form of the penalty
Genetic subtypes example

- Ridge, lasso not quite right

\[ \beta_{12} e_1 + \beta_{13} e_2 \] here meets hypothesis

\[ \beta_{12} e_1 + \beta_{13} e_2 \] here contradicts hypothesis

What matters:
angle \( \alpha \)
Form of the penalty
Genetic subtypes example

• Approach 1
  – Consider \( \alpha \in [0,90] \) degrees
  – Desired orientations are \( \cos(\alpha)=1, \sin(\alpha)=1 \)
  – i.e., goal: minimize \( \cos(\alpha)+\sin(\alpha) \)
  – i.e. minimize
    \[
    \frac{|\beta_{12}| + |\beta_{13}|}{\sqrt{\beta_{12}^2 + \beta_{13}^2}}
    \]
Form of the penalty
Genetic subtypes example

• Approach 2
  - Write $\beta_{12} = p\beta; \beta_{13} = (1-p)\beta$
  - Fit with beta random effect on $p$

  \[ f(p) \]

  \[ 1 \]

  \[ 1 \]

  - Generalization: $\beta = p\beta, p \sim \text{Dirichlet}$
Fitting Approach 2

- E-M algorithm: quite straightforward

- E-step: Computes posterior class membership probabilities given current parameter iterates

- M-step: minimize (e.g. Nelder-Mead)

\[- \sum_{i=1}^{n} \sum_{j=1}^{J} h(j | data) \ln[f_{U|x}(u | x, p, \beta)] + (1 - \frac{\Delta}{2}) \ln[p(1 - p)]\]
Simulation study
Three-class model

• 100 reps; single $x \sim \text{Unif}(-.5,.5); n=1000$
• Poly Log Reg: $\beta_{01} = \beta_{02} = 0$; $\beta_{13} = -1.4$; $\beta_{12} \in \{0, -0.5, -1.4\}$
• Measurement:

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>.15</td>
<td>.85</td>
<td>.85</td>
</tr>
<tr>
<td>.15</td>
<td>.85</td>
<td>.85</td>
</tr>
<tr>
<td>.15</td>
<td>.85</td>
<td>.85</td>
</tr>
<tr>
<td>.15</td>
<td>.13</td>
<td>.85</td>
</tr>
<tr>
<td>.15</td>
<td>.13</td>
<td>.85</td>
</tr>
</tbody>
</table>
Simulation study
Three-class model

• Two assumption scenarios
  – Frank LCR
  – Differential measurement: First three items have increased log(odds =1) per unit x of 1.4 within each class
Simulation study
Beta model: $\Delta = 1.5, .5$

Effectively a 0/1 penalty
Simulation Study
Diff. Meas.; $\beta_{12}=0$; $\beta_{13}=-1.4$

<table>
<thead>
<tr>
<th>Param.</th>
<th>Penalized</th>
<th></th>
<th>LCR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td>$\beta_{12}$</td>
<td>-0.04</td>
<td>0.14</td>
<td>-0.54</td>
<td>0.31</td>
</tr>
<tr>
<td>$\beta_{13}$</td>
<td>-0.79</td>
<td>0.30</td>
<td>-1.01</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Simulation Study
Non-diff meas; $\beta_{12}=0$; $\beta_{13}=-1.4$

<table>
<thead>
<tr>
<th>Param.</th>
<th>Penalized</th>
<th>LCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td>$\beta_{12}$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$\beta_{13}$</td>
<td>-1.42</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Simulation Study
Diff. Meas.; $\beta_{12} = \beta_{13} = -1.4$

<table>
<thead>
<tr>
<th>Param.</th>
<th>Penalized</th>
<th>LCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td>$\beta_{12}$</td>
<td>-1.61</td>
<td>0.32</td>
</tr>
<tr>
<td>$\beta_{13}$</td>
<td>-0.08</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Simulation Study
Non-diff meas; $\beta_{12}=\beta_{13}=-1.4$

<table>
<thead>
<tr>
<th>Param.</th>
<th>Penalized</th>
<th>LCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
</tr>
<tr>
<td>$\beta_{12}$</td>
<td>-1.45</td>
<td>0.34</td>
</tr>
<tr>
<td>$\beta_{13}$</td>
<td>-1.38</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Simulation Study
Non-diff meas; $\beta_{12} = \beta_{13} = -1.4$

\[ \begin{align*}
\text{beta01} & \quad \text{beta02} \\
\text{beta} & \quad \text{p1}
\end{align*} \]
One empirical lead

Deciding the extent of penalization

- Notice the form of $F^*_{v|x}(v|x_i)$:

- Idea 1: Right penalty yields $f^* = f$
Simulation study

Three-class model

- Small: 100 reps; single \( x \sim \text{Unif}(-.5,.5) \)
- Multiple \( n \): Here, \( n = 2000 \)
- Poly Log Reg: \( \beta_{01} = \beta_{02} = 0; \beta_{12} = -1.4; \beta_{12} = -2.8 \)
- Measurement:

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>.15</td>
<td>.85</td>
<td>.85</td>
</tr>
<tr>
<td>.15</td>
<td>.85</td>
<td>.85</td>
</tr>
<tr>
<td>.15</td>
<td>.85</td>
<td>.85</td>
</tr>
<tr>
<td>.15</td>
<td>.13</td>
<td>.85</td>
</tr>
<tr>
<td>.15</td>
<td>.13</td>
<td>.85</td>
</tr>
</tbody>
</table>
Simulation study  
Three-class model

- Two scenarios (among more)
  - Frank LCR
  - **Differential measurement:** last two items have increased log(odds = 1) per unit x of 1.4 within each class

- Premise: \( f_{v|x}^*(v|x_i, \theta) \), \( f_{v|x}^*(v|x_i, \theta) \) quite different

- Measure: Kullback-Leibler distance
### KL Distance: $f^*, f$

**Scenario 1, $n=2000$**

<table>
<thead>
<tr>
<th></th>
<th>-3.4</th>
<th>-3.3</th>
<th>-3.2</th>
<th>-3.1</th>
<th>-3.0</th>
<th>-2.9</th>
<th>-2.8</th>
<th>-2.7</th>
<th>-2.6</th>
<th>-2.5</th>
<th>-2.4</th>
<th>-2.3</th>
<th>-2.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\hat{\beta}_{22}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{\beta}_{12}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.9</td>
<td>4.58</td>
<td>4.28</td>
<td>4.40</td>
<td>4.57</td>
<td>4.19</td>
<td>4.42</td>
<td>4.62</td>
<td>5.09</td>
<td>5.15</td>
<td>5.62</td>
<td>6.03</td>
<td>6.91</td>
<td>7.31</td>
</tr>
<tr>
<td>-1.8</td>
<td>4.52</td>
<td>4.36</td>
<td>4.18</td>
<td>4.07</td>
<td>3.88</td>
<td>3.96</td>
<td>4.22</td>
<td>4.26</td>
<td>4.55</td>
<td>5.09</td>
<td>5.52</td>
<td>5.96</td>
<td>6.58</td>
</tr>
<tr>
<td>-1.7</td>
<td>4.30</td>
<td>4.05</td>
<td>3.90</td>
<td>3.64</td>
<td>3.85</td>
<td>3.71</td>
<td>3.73</td>
<td>4.05</td>
<td>4.35</td>
<td>4.46</td>
<td>4.92</td>
<td>5.33</td>
<td>5.77</td>
</tr>
<tr>
<td>-1.6</td>
<td>4.56</td>
<td>4.21</td>
<td>3.80</td>
<td>3.62</td>
<td>3.52</td>
<td>3.54</td>
<td>3.67</td>
<td>3.69</td>
<td>3.88</td>
<td>4.07</td>
<td>4.36</td>
<td>4.88</td>
<td>5.46</td>
</tr>
<tr>
<td>-1.5</td>
<td>4.67</td>
<td>4.11</td>
<td>3.88</td>
<td>3.70</td>
<td>3.56</td>
<td>3.41</td>
<td>3.46</td>
<td>3.42</td>
<td>3.75</td>
<td>3.74</td>
<td>4.28</td>
<td>4.52</td>
<td>4.85</td>
</tr>
<tr>
<td>-1.4</td>
<td>4.87</td>
<td>4.39</td>
<td>3.91</td>
<td>3.84</td>
<td>3.62</td>
<td>3.27</td>
<td>3.62</td>
<td>3.40</td>
<td>3.69</td>
<td>3.68</td>
<td>3.70</td>
<td>4.03</td>
<td>4.52</td>
</tr>
<tr>
<td>-1.3</td>
<td>5.25</td>
<td>4.73</td>
<td>4.50</td>
<td>4.16</td>
<td>3.86</td>
<td>3.54</td>
<td>3.45</td>
<td>3.46</td>
<td>3.39</td>
<td>3.52</td>
<td>3.78</td>
<td>4.12</td>
<td>4.43</td>
</tr>
<tr>
<td>-1.2</td>
<td>5.58</td>
<td>4.99</td>
<td>4.76</td>
<td>4.47</td>
<td>4.16</td>
<td>3.81</td>
<td>3.70</td>
<td>3.60</td>
<td>3.75</td>
<td>3.74</td>
<td>3.85</td>
<td>4.25</td>
<td>4.30</td>
</tr>
<tr>
<td>-1.1</td>
<td>6.25</td>
<td>6.05</td>
<td>5.26</td>
<td>4.90</td>
<td>4.55</td>
<td>4.14</td>
<td>4.20</td>
<td>4.03</td>
<td>4.01</td>
<td>3.94</td>
<td>3.91</td>
<td>4.45</td>
<td>4.28</td>
</tr>
</tbody>
</table>

**ML**

**True**
KL Distance: $f^*, f$

Scenario 2, $n=2000$

<table>
<thead>
<tr>
<th>$\hat{\beta}_{22}$</th>
<th>-3.8</th>
<th>-3.7</th>
<th>-3.6</th>
<th>-3.5</th>
<th>-3.4</th>
<th>-3.3</th>
<th>-3.2</th>
<th>-3.1</th>
<th>-3.0</th>
<th>-2.9</th>
<th>-2.8</th>
<th>-2.7</th>
<th>-2.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\hat{\beta}_{12}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2.4</td>
<td>4.03</td>
<td>4.37</td>
<td>4.63</td>
<td>5.05</td>
<td>5.39</td>
<td>5.93</td>
<td>6.35</td>
<td>7.17</td>
<td>8.00</td>
<td>8.76</td>
<td>9.36</td>
<td>10.40</td>
<td>11.74</td>
</tr>
<tr>
<td>-2.3</td>
<td>3.79</td>
<td>3.87</td>
<td>4.10</td>
<td>4.59</td>
<td>4.93</td>
<td>5.14</td>
<td>5.84</td>
<td>6.38</td>
<td>6.76</td>
<td>7.79</td>
<td>8.55</td>
<td>9.46</td>
<td>10.50</td>
</tr>
<tr>
<td>-2.2</td>
<td>3.48</td>
<td>3.63</td>
<td>3.90</td>
<td>3.98</td>
<td>4.27</td>
<td>4.60</td>
<td>5.20</td>
<td>5.76</td>
<td>6.17</td>
<td>7.01</td>
<td>7.78</td>
<td>8.26</td>
<td>9.65</td>
</tr>
<tr>
<td>-2.1</td>
<td>3.31</td>
<td>3.17</td>
<td>3.47</td>
<td>3.51</td>
<td>3.95</td>
<td>4.25</td>
<td>4.69</td>
<td>5.04</td>
<td>5.64</td>
<td>6.34</td>
<td>7.01</td>
<td>8.09</td>
<td>9.07</td>
</tr>
<tr>
<td>-2.0</td>
<td>3.19</td>
<td>3.29</td>
<td>3.41</td>
<td>3.33</td>
<td>3.70</td>
<td>3.94</td>
<td>4.34</td>
<td>4.60</td>
<td>5.10</td>
<td>5.62</td>
<td>6.70</td>
<td>7.24</td>
<td>8.07</td>
</tr>
<tr>
<td>-1.8</td>
<td>3.31</td>
<td>3.24</td>
<td>3.22</td>
<td>3.26</td>
<td>3.35</td>
<td>3.63</td>
<td>3.98</td>
<td>4.35</td>
<td>4.75</td>
<td>5.12</td>
<td>5.34</td>
<td>6.40</td>
<td>7.00</td>
</tr>
<tr>
<td>-1.7</td>
<td>3.56</td>
<td>3.33</td>
<td>3.43</td>
<td>3.32</td>
<td>3.31</td>
<td>3.57</td>
<td>3.85</td>
<td>4.17</td>
<td>4.40</td>
<td>4.79</td>
<td>5.43</td>
<td>6.00</td>
<td>6.33</td>
</tr>
<tr>
<td>-1.6</td>
<td>3.83</td>
<td>3.77</td>
<td>3.60</td>
<td>3.69</td>
<td>3.68</td>
<td>3.62</td>
<td>3.80</td>
<td>4.19</td>
<td>4.65</td>
<td>4.87</td>
<td>5.38</td>
<td>6.21</td>
<td>6.62</td>
</tr>
<tr>
<td>-1.5</td>
<td>4.36</td>
<td>3.95</td>
<td>4.02</td>
<td>3.97</td>
<td>3.89</td>
<td>3.82</td>
<td>4.05</td>
<td>4.24</td>
<td>4.56</td>
<td>5.05</td>
<td>5.37</td>
<td>5.86</td>
<td>6.36</td>
</tr>
<tr>
<td>-1.4</td>
<td>4.90</td>
<td>4.69</td>
<td>4.43</td>
<td>4.28</td>
<td>4.34</td>
<td>4.46</td>
<td>4.35</td>
<td>4.65</td>
<td>4.88</td>
<td>5.11</td>
<td>5.41</td>
<td>5.99</td>
<td>6.49</td>
</tr>
<tr>
<td>-1.3</td>
<td>5.56</td>
<td>5.41</td>
<td>5.11</td>
<td>4.95</td>
<td>4.77</td>
<td>4.84</td>
<td>4.72</td>
<td>4.74</td>
<td>5.01</td>
<td>5.49</td>
<td>5.85</td>
<td>6.19</td>
<td>6.60</td>
</tr>
<tr>
<td>-1.2</td>
<td>6.41</td>
<td>5.97</td>
<td>5.87</td>
<td>5.59</td>
<td>5.37</td>
<td>5.17</td>
<td>5.33</td>
<td>5.18</td>
<td>5.52</td>
<td>5.96</td>
<td>6.08</td>
<td>6.31</td>
<td>6.99</td>
</tr>
</tbody>
</table>
Simulation Study
Empirical support for "penalty"?

- Average conditional probability estimates amazingly stable

- Distinction: Y|V*, x
Frailty analysis: Data
InCHIANTI \textit{(Ferrucci et al., JAGS, 48:1618-25)}

- **Aim**: Causes of walking decline

- **Brief design**
  - Random sample \( \geq 65 \) years \( n=1270 \)
  - Enrichment for oldest-old, younger ages
  - Participation: > 90\% in the primary sample
  - Home interview, blood draw, physical exam

- **Dysregulation**: Inflammation – 7 cytokines
  - \textit{IL-6, CRP, TNF-\( \alpha \), IL-1RA, IL-18, IL-1B, TGF-\( \beta \)}
  - Here: concern = poorer inhibition

- **Frailty**: Fried criteria (as before)
Frailty analysis: Results

- Measurement model: 2 classes
  - Conditional probabilities similar to WHAS
  - Lower “frail” prevalence (15% vs. 27%)

- Regression model
  - 1 SD worse inhibition index associated with 35% reduction in non-frail odds ($z \sim 3$)
  - Regression coefficient on original index scale: 3.00

- Next: Vary regression coefficients in increments of +/- 0.5, up to +/- 2.0
Frailty analysis: Results
Posterior probs. from different fits
Frailty analysis: Results
Posterior probs. non-frail, different fits
# Frailty analysis: Results

**Age-adjusted relation to mobility**

<table>
<thead>
<tr>
<th>Frailty fit: inflamm. slope</th>
<th>Mobility slope (frail vs non)</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML – 2.0</td>
<td>-1.1</td>
<td>.089</td>
</tr>
<tr>
<td>ML – 1.0</td>
<td>-1.0</td>
<td>.087</td>
</tr>
<tr>
<td>ML – 0.5</td>
<td>-1.0</td>
<td>.086</td>
</tr>
<tr>
<td>ML</td>
<td>-0.99</td>
<td>.085</td>
</tr>
<tr>
<td>ML + 0.5</td>
<td>-0.93</td>
<td>.085</td>
</tr>
<tr>
<td>ML + 1.0</td>
<td>-0.92</td>
<td>.085</td>
</tr>
<tr>
<td>ML + 2.0</td>
<td>-0.82</td>
<td>.083</td>
</tr>
</tbody>
</table>
Recap

• Presented: Frameworks for measurement
  – of complex geriatric health states
  – incorporating biological knowledge

• Demonstrations
  – Frailty in WHAS
  – Frailty and inflammatory dysregulation in In CHIANTI
Rationale for the proposal

• vs looser internal validation criteria?
  – estimability

• vs Bayesian approach
  – depends on degree of empiricism
  – if balance by “consensus”—Bayesian

• Allows some distrust of the data
Research needed

- Theory elicitation, incorporation

- Methodology freeing measurement model estimation to “move” with “penalty”
  - Rotation?
  - Penalty on conditional probabilities

- Compromise of latent variable, predictive approaches

- Best index derivation
Implications

• Refined understanding of aging states and their measurement
  – Integrating biology
  – Increasing sensitivity, specificity

• Heightened accuracy, precision for
  – Delineating etiology
  – Developing and targeting interventions
Acknowledgments

• Hopkins Colleagues
  Linda Fried, Ron Brookmeyer, Yi Huang, Jeannie-Marie Leoutsakos, Jeremy Walston, Qian-Li Xue, Scott Zeger

• Colleagues outside of Hopkins
  Luigi Ferrucci, Jack Guralnik, Don Ingram, Richard Miller

• Funding / Institutional Support
  Johns Hopkins Older Americans Independence Center, National Institute on Aging, Alliance for Aging Research